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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/511,776	02/24/2000	Roger K Craig	4256/86197	5653

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EXAMINER
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GABEL, GAILENE

ART UNIT	PAPER NUMBER
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1641

DATE MAILED: 11/27/2001

9

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

09/511,776

Applicant(s)

CRAIG ET AL.

Examiner

Gailene R. Gabel

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 04 September 2001.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1,2,4-8 and 10-22 is/are pending in the application.
- 4a) Of the above claim(s) 15-18 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,2,4-8 and 19-22 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☒ Claim(s) 1-2, 4-8, 10-22 are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

### Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

### Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

## **DETAILED ACTION**

### ***Amendment Entry***

1. Applicant's amendment and response filed 9/4/01 in Paper No. 8 is acknowledged and has been entered. Applicant's submission of Rule 1.132 declaration by Dr. Woolfson is also acknowledged. Claims 1-2, 4-7, 10-11, 13-14, 19-20, and 22 have been amended. Claims 3 and 9 have been cancelled. Accordingly, claims 1-2, 4-8, and 10-22 are pending. Claims 1-2, 4-8, 10-14 and 19-22 are under examination.

### **Rejections Withdrawn**

#### ***Claim Rejections - 35 USC § 112/102/103 Double Patenting***

2. Rejections of claims 3 and 9 are now moot in light of Applicant's cancellation of the claims.

3. In light of Applicant's amendment and argument, the rejection of claims 2, 7-8, 10-11, and 14 under 35 U.S.C. 102(e) as being anticipated by Epps et al. (US 6,203,994) is, hereby, withdrawn.

4. In light of Applicant's amendment and argument, the rejection of claims 2, 5-8, and 11 under 35 U.S.C. 102(e) as being anticipated by Eberwine et al. (WO 96/05847) is, hereby, withdrawn.

5. In light of Applicant's amendment and argument, the rejection of claims 10-11 and 14 under 35 U.S.C. 103(a) as being unpatentable over Prusiner et al. (US 5,891,641), Martinez et al. (WO 98/41872), or Eberwine et al. (WO 96/05847) in view of

Epps et al. (US 6,203,994) or Kinjo et al. (Nucleic Acids Research, 1995) is, hereby, withdrawn.

6. In light of Applicant's amendment and argument, the rejection of claims 19-22 under 35 U.S.C. 103(a) as being unpatentable over Eberwine et al. (WO 96/05847) or Epps et al. (US 6,203,994) in view of Foster et al. (US 4,444,879) is, hereby, withdrawn.

**Rejections Maintained**

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-2, 4-8, and 10-14, as amended, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite in reciting, "detecting said protein by the binding of said labeled first binding partner **or** said labeled second binding partner" because it is unclear how detection is differentially effected based on which binding partner the protein binds to, i.e. first, which is conformational state dependent or second, which is not conformational state dependent. Claim 1 is incomplete in lacking a correlation step that differentially relates binding of the protein with either the first binding partner or the second binding partner so as to determine the conformational state of the protein as required by the preamble of the claim. See also claims 5 and 13.

Claim 2 is incomplete in lacking a correlation step that structurally and functionally relates the binding of the protein with the first binding partner and the second binding partner with the post translational modification activity of the enzyme so as to measure or determine post translational modifying activity of the enzyme as required by the preamble. See also claims 5 and 13.

Claim 5 lacks antecedent support in reciting, "said protein that does not bind to said capture ligand".

Claim 13 is vague and indefinite in reciting, "unbound labeled first binding partner is removed" because it is unclear how "removal or separation" of unbound components is effected based on the limitations set forth in claims 1 or 2 from which it depends from, as currently recited.

### ***Double Patenting***

8. Claims 1, 4-8, 10-14 and 19-22 stand provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-13 and 18-21 of copending Application No. 09/258,452 for reason of record. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Specifically, claims 1-13 and 18-21 of ASN 09/258,452 do not appear to exclude that the binding or coupling of the protein with the first binding partner or the second binding partner is not covalent.

### ***Claim Rejections - 35 USC § 102/103***

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9. Claims 1, 4-8, and 12-13 stand rejected under 35 U.S.C. 102(e) as being anticipated by Prusiner et al. (US 5,891,641) for reason of record.
10. Claims 1, 4-8, and 12-13 stand rejected under 35 U.S.C. 102(e) as being anticipated by Martinez et al. (WO 98/41872) for reason of record.
11. Claims 1, 7-8, and 10-11 stand rejected under 35 U.S.C. 102(e) as being anticipated by Tsien et al. (US 5,998,204) for reason of record.
12. Claims 19-22 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Prusiner et al. (US 5,891,641) or Martinez et al. (WO 98/41872) or Tsien et al. (US 5,998,204) in view of Foster et al. (US 4,444,879) for reason of record.

**New Grounds of Rejection**

**New Matter**

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1, 4-8, 10-14, and 19-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In this case, the specification does not appear to provide any literal support for the recitation of "said protein and said labeled first binding partner or said second binding partner are not covalently coupled". Page 4, second full paragraph describes association and binding between protein and binding partners but fails to provide literal support for such recitation. Furthermore, none of the originally filed claims recited the limitation in question. Recitation of claim limitation lacking literal support in the specification or originally filed claims constitutes new matter.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

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consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 2 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over 1) Prusiner et al. (US 5,891,641) or Martinez et al. (WO 98/41872) and 2) Tsien et al. (US 5,998,204) in view of 3) Eberwine et al. (WO 96/05847) and 4) Epps et al. (US 6,203,994) or Kinjo et al. (Nucleic Acids Research, 1995).

Prusiner et al., Martinez et al., and Tsien et al. have been discussed in Paper No. 7.

Prusiner, Martinez, and Tsien differ in failing to disclose measuring enzyme activity wherein the conformation of a protein is dependent upon post-translational modification activity of the enzyme. Further, Prusiner et al. and Martinez et al. differ in failing to use fluorescence resonance energy transfer (FRET) or fluorescence correlation spectroscopy (FCS) to measure binding between proteins and binding partners. Tsien et al. differs in failing to use FCS to measure binding between proteins and binding partners.

Eberwine et al., Epps et al., and Kinjo et al. have been discussed in Paper No. 7.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to apply the teaching of Eberwine and Epps in measuring post-translational modification activity of enzymes in the methods of Prusiner, Martinez, and Tsien because enzyme activity are known to mediate conformational changes in proteins and the disclosed methods of Prusiner, Martinez, and Tsien are generic with respect to the type of protein being assayed for binding. Further, it would have been



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obvious to one of ordinary skill in the art at the time of the instant invention to have substituted another known applicable detection method such as FCS as taught by Kinjo and Epps into the methods of Prusiner, Martinez, Tsien, and also Eberwine because Tsien specifically used FRET for detection and Epps and Kinjo specifically taught that FRET and FCS are used to monitor ligand interaction kinetics; therefore, FRET or FCS constitute an obvious design choice for detection of binding between proteins and binding partners.

### ***Response to Arguments***

15. Applicant's arguments filed 9/4/01 have been fully considered but they are not persuasive.

A) Applicant argues that Prusiner does not teach all the elements of claim 1 and therefore, does not anticipate claims 1, 4-8, and 12-13 of the instant application. Specifically, Applicant argues that Prusiner discloses contacting a protein in a first conformation with a labeled antibody and contacting the protein in a second conformation with the same labeled antibody.

In response, claim 1 as currently recited does not exclude that the second labeled antibody is distinct from the first labeled antibody. Further, Prusiner teaches application of his invention in a sandwich format for added sensitivity wherein a capture ligand or capture antibody (second antibody) binds the protein into solid phase substrate and the binding is not dependent on the conformational state of the protein;

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thus, inherently teaching a distinct second capture antibody from the first labeled antibody (see column 16, lines 24-37).

B) Applicant argues that Martinez does not teach all the elements of claim 1 and therefore, does not anticipate claims 1, 4-8, and 12-13 of the instant application. Specifically, Applicant argues that Martinez discloses (a sandwich format assay) contacting a protein with a labeled first antibody and a second unlabeled antibody.

Contrary to Applicant's argument, Martinez, indeed, discloses contacting the protein with a biotin-labeled first antibody and a second enzyme-labeled (PO or peroxidase) antibody in page 7, lines 10-30 such as recited in the claimed invention.

C) Applicant argues that Tsien does not teach all the elements of claim 1 and therefore, does not anticipate claims 1, 7-8, and 10-11 of the instant application. Specifically, Applicant argues that Tsien requires that the donor fluorescent protein and the acceptor fluorescent protein are covalently coupled to the binding protein moiety whereas the claimed invention requires that the first and second binding partners are not covalently coupled. Further, Applicant argues that Tsien does not teach use of FCS.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., Tsien et al. do not teach use of FCS or fluorescence anisotropy) are not recited in the rejected claims. Although the claims are interpreted in light of the specification,

limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Contrary to Applicant's argument, Tsien does **not** require covalent coupling and rather teaches against covalent coupling (see especially column 5, lines 22-27). Specifically, Tsien discloses that "ligand induced conformational changes can be monitored by FRET ... if the binding protein is fused to a donor and acceptor GFP. This approach has several advantages over the usual covalent labeling with fluorescent probes."

D) Applicant argues that Prusiner, Martinez, and Tsien do not teach or suggest all the limitations recited in claims 19 and 20. Further, Applicant argues that none of Prusiner, Martinez, or Tsien in combination with Foster suggest all the elements of claims 19-22 and therefore, would not provide the kit taught in the claimed invention

In response, Prusiner, Martinez, and Tsien have been discussed in paragraphs 15A), 15B), and 15C). Prusiner teaches application of his invention in a sandwich format for added sensitivity wherein a capture ligand or capture antibody (second antibody) binds the protein into solid phase substrate and the binding is not dependent on the conformational state of the protein; thus, inherently teaching a distinct second capture antibody from the first labeled antibody. Martinez discloses contacting the protein with a biotin-labeled first antibody and a second enzyme-labeled (PO or peroxidase) antibody such as recited in the claimed invention. Tsien does **not** require covalent coupling and discloses that "ligand induced conformational changes can be

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monitored by FRET ... if the binding protein is fused to a donor and acceptor GFP. This approach has several advantages over the usual covalent labeling with fluorescent probes." It would, therefore, have been obvious to have incorporated the protein standards, binding partners and label reagents taught by Prusiner, Martinez, and Tsien into a kit format such as in the teaching of Foster for use in their respective methods because kit formats are recognized for their advantage in convenience and economy.

16. No claims are allowed.

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

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18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday to Thursday, 6:30 AM - 4:00 PM and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (703) 308-3399. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



grg  
November 18, 2001



LONG V. LE  
SUPERVISORY PATENT EXAMINER  
TECHNOLOGY CENTER 1600

11/19/01